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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD,
Patent Owner.

Case IPR2017-02106
Patent No. 9,067,992

PATENT OWNER'S PRELIMINARY RESPONSE

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2001	D. van der Heijde et al., *Psoriatic arthritis imaging: a review of scoring methods*, 64 (Suppl. II) ANN RHEUM DIS ii61-ii64 (2005)
2002	Information Disclosure Statement dated February 6, 2015, submitted during prosecution of U.S. Application No. 14/563,056
2003	Christopher Ritchlin et al., *Patterns of Cytokine Production in Psoriatic Synovium*, 25 J OF RHEUMATOLOGY 1544-52 (1998)
2004	Elli Kruithof et al., *Synovial histopathology of psoriatic arthritis, both oligo- and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis*, 7 ARTHRITIS RESEARCH & THERAPY R569-R580 (2005)
2005	Dafna D. Gladman, *Effectiveness of Psoriatic Arthritis Therapies*, 33 SEMIN ARTHRITIS RHEUM 29-37 (2003)
2006	Andreea Coca & Christopher T. Ritchlin, *Psoriatic arthritis: Expanding therapeutic options*, 28 THE JOURNAL OF MUSCULOSKELETAL MEDICINE 163-70 (2011)
2007	Irwin M. Freedberg et al. (eds.), FITZPATRICK'S DERMATOLOGY IN GENERAL MEDICINE (6th edition, 2003)
2008	John Brockbank & Dafna Gladman, *Diagnosis and Management of Psoriatic Arthritis*, 62 DRUGS 2447-57 (2002)
2009	John Brockbank & Dafna Gladman, *Psoriatic Arthritis*, 9 EXPERT OPINION ON INV. DRUGS 1511-22 (2000)
2010	KINERET® (anakinra) Package Insert (May 2016)
2011	A. Gibbs et al., *Efficacy of anakinra (Kineret) in psoriatic arthritis: A Clinical and Immunohistological Study*, 65 (Suppl. II) ANN RHEUM DIS. 216 (2006)
2012	P. Madureira et al., *Off-label use of tocilizumab in psoriatic arthritis: case series and review of the literature*, 41 ACTA REUMATOL PORT. 251-255 (2016)
2013	William J. Sandborn et al., *A Randomized, Double-Blind, Placebo-Controlled Trial Of Subcutaneous Etanercept (p75 Soluble Tumor Necrosis Factor:FC Fusion Protein) ln The Treatment Of Moderate To Severe Crohn's Disease*, 120 GASTROENTEROLOGY, A-20 (April 2001)
2014	*Will Onercept failure derail similar biologics?*, FROST & SULLIVAN (May 5, 2005), http://www.frost.com/sublib/display-market-insight.do?id=37506280

EXHIBIT	DESCRIPTION
2015	Lisa M. Sedger et al., *Therapeutic Antibody-Based Drugs in the Treatment of Human Inflammatory Disorders*, IMMUNOLOGY AND MICROBIOLOGY (Krassimir Metodiev, ed. April 26, 2017)
2016	*Pegsunercept*, ADIS R&D INSIGHT (Dec. 21, 2010) *downloaded* on December 14, 2017
2017	Dennis McGonagle et al., *Psoriatic Arthritis: A Unified Concept Twenty Years On*, 42 ARTHRITIS & RHEUMATISM 1080-86 (1999)
2018	The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group, *Etanercept plus Standard Therapy for Wegener's Granulomatosis*, 352 N ENGL J MED 351-61 (2005)
2019	Simon Bowers, *Celltech hit by failure of Crohns disease drug*, THE GUARDIAN (LONDON) 14 (2003)
2020	J Bauditz et al., *Treatment with tumour necrosis factor inhibitor oxpentifylline does not improve corticosteroid dependent chronic active Crohn's disease*, 40 GUT 470-474 (1997)
2021	Trexall Tablets, Approval Package for Application Number ANDA 40-385 (2001)
2022	Letter from Bob A. Rappaport, FDA, to James D. Steck, Abbott Laboratories (Nov. 9, 2006) (on file with the FDA)
2023	Charles Camisa, M.D., HANDBOOK OF PSORIASIS, Blackwell Publishing, Inc. (MA) (2004)

I. Introduction

U.S. Patent No. 9,067,992 (the "'992 patent") discloses the innovative work of AbbVie scientists to develop novel methods of treating psoriatic arthritis ("PsA") with the biologic drug HUMIRA® (adalimumab). The claimed dosing regimen includes a subcutaneous dose of 40 mg of adalimumab every-other-week.

Petitioner has failed to show that, in view of the prior art, a person of ordinary skill in the art ("POSA") would have reasonably expected that adalimumab would treat PsA at all, much less that it would be effective using the claimed 40 mg every-other-week dosing regimen. Petitioner's two obviousness challenges therefore fail to establish a reasonable expectation of success.

Notably, Petitioner's obviousness grounds do not include any prior art disclosure of the use of adalimumab to treat PsA. Instead, Petitioner argues that experience with *other drugs* would have led to a reasonable expectation that adalimumab would treat PsA because adalimumab had been approved to treat rheumatoid arthritis ("RA"). But PsA and RA are different diseases affecting different tissues. Whereas RA mainly affects the synovium of certain joints, PsA affects not only the synovium of the joints affected by RA, but also different joints, the entheses (the connections between the joints and the tendons), nails, spine, and the largest organ in the body, the skin. The differences between the two diseases are confirmed by the fact that multiple drugs approved to treat RA are not

indicated for, or are contraindicated in, PsA. Further, Petitioner does not compare the distribution or pharmacokinetics of adalimumab in tissues affected by PsA to those of any other anti-TNFα agent. As a result, Petitioner has not established that experience with other anti-TNFα agents would give a POSA a reasonable expectation that adalimumab would be successful to treat PsA.

Petitioner also fails to establish that a POSA would have had a reasonable expectation that the same dose of adalimumab approved to treat RA would effectively treat PsA. Petitioner's cited references confirm the uncertainty regarding the dosing of other TNFα inhibitors in the art. For example, Petitioner relies on art related to infliximab that shows that infliximab was administered using a dose of 5 mg/kg to treat PsA rather than the 3 mg/kg dose approved to treat RA. Likewise, methotrexate, a small molecule drug used to treat PsA, was used at a different dose for PsA than for RA. Thus, Petitioner's premise that a POSA would simply use the same dose for PsA as the dose used for RA is inconsistent with the varying doses used in the art for other TNFα inhibitors.

Petitioner's obviousness arguments are particularly deficient with respect to dependent claim 7. Claim 7 recites a method of reducing or inhibiting the progression of structural damage in PsA as assessed by radiograph. This outcome addresses a serious symptom of PsA, the destruction of the patient's joints. For this claim, Petitioner's cursory analysis does not cite disclosure of *any agent* (small

molecule or biologic) that successfully inhibited the progression of structural damage in PsA. Indeed, Petitioner ignores express statements in its cited references that the ability of an anti-TNFα agent to successfully inhibit progression of structural damage required further study. Petitioner's conclusory argument that because adalimumab and infliximab inhibited progression of structural damage in *RA*, one of skill would expect it to do so in *PsA* is unsupported and thus fails to establish a reasonable expectation of success.

Finally, for a subset of the challenged claims, Petitioner offers an anticipation ground that is inconsistent with its other positions. Petitioner argues that the language of claims 1, 5, and 6, which recite achievement of certain efficacy outcomes, does not limit the claims, but simultaneously argues that the presence of those same outcomes necessitates a later priority date. Petitioner's inconsistency warrants denial of its anticipation ground.

For these and the additional reasons below, Petitioner has failed to meet its burden of showing a reasonable likelihood that it will prevail as to any challenged claim. The Board should therefore deny institution of the Petition.

II. Background

A. Psoriatic Arthritis

PsA is an autoimmune inflammatory disorder that affects the ligaments, tendons, entheses (the tissue that connects tendons to joints), and spinal or

peripheral joints. (Ex. 2007, 42; Ex. 2009, 1511-12.)[1] Although PsA is a separate condition from psoriasis, most patients who suffer from PsA also develop some severity of psoriasis, and in treating PsA, "[a]ny treatment for the arthritis must also help the skin." (Ex. 2009, 1511; Ex. 2008, 2449, 2455.) PsA's etiology and pathogenesis are unknown. (Ex. 2009, 1512.) In addition, "[w]ide variability in disease between patients" makes it difficult to study drug efficacy in PsA. (*Id.*, 1519.)

In its most severe form, psoriatic arthritis can result in the destruction of a patient's joints. (*Id.*, 1514.) As of 2000, structural damage caused by the disease measured by radiographic imaging was known to occur in destructive forms that could progress rapidly but were poorly understood. (*Id.*, 1519.) PsA patients can also experience joint fusion (ankylosis), destruction of bone cells (bone lysis), and new bone formation that are collectively "responsible for a large degree of the long-term loss of function and disability" and are "very particular to PsA." (*Id.*)

Various scoring methods had been developed to use radiographic imaging to determine if structural damage was progressing in RA patients, including the "Sharp score." (Ex. 2001, ii61-62.) However, distinct systems were needed for PsA

[1] Citations refer to the original page numbering of each exhibit except for references that have been stamped with page numbers. Citations to such references refer to the stamped-on page numbers.

patients to account for the difference in radiographic damage in PsA patients compared to that in RA patients. (*Id.*). Such PsA methods include a modified Sharp Score, (also referred to as "mTSS" or modified total Sharp score), Modified Steinbrocker Score, Van der Heijde Modified Score, and PsA Ratingen Score. (*See, e.g.*, *id.*, ii61-64; Ex. 1001, 37:55.) The modified Sharp score for PsA, for example, includes additional erosion scale scores to account for the potential for more extensive bone destruction in PsA than RA, and scoring for particular features only seen in PsA patients. (*See* Ex. 2001, ii62.)

Historically, inhibition of the progression of structural damage caused by PsA was a difficult endpoint to achieve. Petitioner has cited no reference discussing that a treatment (small molecule or biologic) successfully reduced or inhibited structural damage in PsA patients. Petitioner also ignores examples of treatments that did not achieve that endpoint. For example, although methotrexate was shown to effectively treat PsA, a study reported that "[n]o improvement in radiographic progression was evident after treatment with methotrexate for 2 years compared with placebo." (Ex. 1023, 5; *see also* Ex. 2008, 2451.)

B. Rheumatoid Arthritis and Psoriatic Arthritis Are Different Diseases

PsA and RA are distinct diseases: they affect different tissues, have different pathologies, result in different symptoms, have different subtypes, and cause different deformities.

PsA and RA Affect Different Tissues. Whereas RA affects the synovium of the joints, PsA not only affects a patient's joints, but can also affect his or her entheses (the tissue that connects tendons to joints), spine, nails, and skin. (Ex. 2008, 2450; Ex. 2003, 1544; Ex. 1023, 2.) For example, PsA patients frequently have spinal involvement, whereas RA patients do not. (Ex. 2008, 2450.) While researchers acknowledge PsA, like RA, involves impairment of the joints, some suggest that PsA is primarily driven by enthesopathic disorder—inflammation of the entheses. (*Id.*, 2450-51 (citing Ex. 2017, 1080-86).)

The Pathology of PsA Is Different than RA. The pathology of PsA is poorly understood. Nonetheless, the pathology of PsA has been shown to be different from RA. For example, in a 2004 publication, a group of scientists compared synovial fluid in PsA patients to that from patients with spondyloarthropathy ("SpA") and patients with rheumatoid arthritis. (Ex. 2004, R569.) The study found that PsA synovial fluid more closely resembled synovial fluid from SpA patients than RA patients and found multiple differences between RA and PsA synovial fluid. (*Id.*, R569, R576-78.)

PsA Has a Different Cytokine Profile than RA. Some scientists have found that the presence of TNFα in synovial fluid is higher in PsA patients than in RA patients. (Ex. 2003, 1544.) Moreover, more CD8+ T cells are present in PsA synovial fluid, whereas RA has more CD4+ T cells. (Ex. 2008, 2451.)

PsA and RA Patients Experience Different Clinical Symptoms. PsA patients frequently have involvement of distal interphalangeal joints (certain joints of the hands and feet) and asymmetric joint involvement, whereas RA patients typically do not. (*Id.*, 2449; Ex. 2009, 1511.) Unlike in RA, dactylitis—the swelling of an entire digit—and "ray" joint distribution—disease effect in all joints in a single digit—are common in PsA patients. (Ex. 2008, 2449.) And, unlike RA, PsA is defined not just by its effect on a patient's joints, but also by its association with psoriasis. (Ex. 2009, 1512.)

Joint Disease in PsA Is Heterogeneous. With respect to joint disease, PsA patients can have one of multiple different subtypes of disease in their joints, including arthritis of the distal interphalangeal joints (affecting hands, feet, or both), arthritis mutilans (deforming and destructive subtype involving bone resorption or osteolysis), symmetric polyarthritis (larger number of affected joints), asymmetric oligoarthritis (smaller number of affected joints), and/or spondyloarthropathy (affecting the spine and sacroiliac joints). (Ex. 2009, 1512.) This heterogeneity of the PsA patient population distinguishes it from RA, which primarily is restricted to localized inflammation of peripheral joint synovial linings. (Ex. 1023, 1-2; Ex. 2017, 1082.)

PsA Patients Experience Different Deformities than RA Patients. PsA patients also exhibit different deformities and radiographic manifestations of

disease than RA patients. (Ex. 2008, 2450.) RA may display certain deformities in joints in the hands (referred to as "swan necking" or "boutonniere" deformities); PsA patients, in contrast, display rigid stiffening (ankylosis) of joints and shortening (telescoping) or floppy (flailing) digits. (*Id*.) Moreover, radiographs of PsA patients show erosive disease of the DIP joints, new bone formation (periostitis), spurs of the entheses (connections of tendon to bone), or a deformity in which digits appear to fit together like a pencil in a cup. (*Id*.) These radiographic features are not present in RA patients. (*Id*.) Indeed, "ankylosis, bone lysis [destruction of bone cells] and new bone formation are very particular to PsA and not commonly seen in RA," and "are responsible for a large degree of the long-term loss of function and disability in [PsA] patients." (Ex. 2009, 1519.)

C. Treatments for RA and PsA Are Different

Because "PsA and RA are distinct diseases," Gladman noted that the efficacy and safety of an agent in RA versus PsA cannot be assumed to be the same. (Ex. 2005, 29.) With respect to the ankylosis, bone lysis, and new bone formation that are unique to PsA and responsible for long-term disability in PsA patients, it was acknowledged in the art that "specific new therapies above those developed for RA" could be required to manage the problems with PsA. (Ex. 2009, 1519.)

The authors of the references cited by Sandoz concluded that "[t]he response to therapy" for PsA that is "derived from clinical experience in [RA]" is "often unsatisfactory." (Ex. 1017, 2.) Indeed, at the time of the invention, it was known that multiple treatments that are effective in RA are not effective in treating PsA. For example, among small molecule treatments, gold and sulfasalazine are common treatments for RA, but were cited in Petitioner's asserted prior art (Mease 2000) as having "[f]ew or no benefits" in PsA. (Ex. 1017, 6; *see also* Ex. 2005, 32-33.) And corticosteroids, cited by Petitioner for their use in RA (Pet., 40, Table 3; Ex. 1002, ¶ 112, Table 2), were "contraindicated in patients with PsA" because of their potential to cause serious side effects in the skin. (Ex. 2009, 1515; *see also* Ex. 2023, 6; Ex. 2008, 2453.) Similarly, hydroxychloroquine is considered suitable for treating RA, but can exacerbate skin lesions in PsA patients and has been associated with precipitating pustular psoriasis. (Ex. 1023, 3.)

There are also multiple biologics that have not been shown to be effective in treating PsA, despite being effective for RA. For example, rituximab is effective in treating RA, but studies have failed to show it has efficacy in treating PsA. (*See* Ex. 2006, 4, 5.) And both anakinra and tocilizumab are approved for use in RA, but have shown limited improvement in patients with PsA and have shown some evidence of worsening the disease. (Ex. 2010, 1; Ex. 2011, 216; Ex. 2012, 255.)

III. The Asserted References

A. Keystone (Ex. 1003)

The Keystone abstract discusses the use of 20, 40, or 80 mg of adalimumab every-other-week for treating RA. (*See* Ex. 1003.) The population of patients studied in Keystone included "76.8% females [and] 81% rheumatoid factor positivity." (*Id.*, A481.) Keystone does not discuss PsA or adalimumab's effect on, or distribution to, all of the tissues affected by PsA, much less a dosing regimen for treating patients with that condition. Keystone also does not discuss whether adalimumab inhibits progression of structural damage in any disease.

B. Lorenz (Ex. 1028)

Lorenz provides an overview of clinical trials using infliximab and/or etanercept to treat different TNFα-mediated conditions, including RA, Crohn's disease, juvenile chronic arthritis, psoriasis, PsA, ankylosing spondylitis, adult-onset Still's disease, polymyositis, dermatomyositis, Behçet's disease, and Wegener's granulomatosis. (*See generally* Ex. 1028.)

Lorenz never discusses adalimumab (also referred to as D2E7) in connection with PsA. (*See* Ex. 1028, S17-19.) It also does not disclose any clinical trials, dosage, or results for adalimumab in the treatment of PsA. (*See generally* Ex. 1028.) Rather, Lorenz speculates that "encouraging results might arise" if TNFα-directed agents, such as etanercept, onercept, PEG-TNFRI ("pegsunercept"), and adalimumab, were to be used in trials for other non-specified TNFα-associated

conditions. (*Id.*, S17-18.) Lorenz cautions, however, that that further studies of the efficacy of these agents "are required" and that such studies should "focus[] particularly on radiological progression … in patients with RA," both for etanercept and D2E7. (*Id.*, S18.)

The need for this caution was illustrated by known failures of various anti-TNFα biologics to treat specific TNFα-mediated diseases. Sandborn, for example, reported in 2001 that etanercept failed to treat Crohn's disease. (Ex. 2013, 6.) Further, Phase 3 trials of onercept in psoriasis were later discontinued and the drug was never approved for this indication. (Ex. 2014, 1.) Similarly, pegsunercept was never approved for psoriasis. (*See generally* Ex. 2016.)

Lorenz discusses clinical trials using 5 or 10 mg/kg of infliximab or 25 mg twice a week of etanercept to treat PsA patients. (Ex. 1028, S18-19.) Lorenz does not disclose using the approved RA dose for infliximab (3 mg/kg) to treat PsA. Nor does it disclose or suggest a dosing regimen for adalimumab, any connection between adalimumab and PsA, or whether adalimumab could inhibit the progression of structural damage in PsA patients. Lorenz also does not disclose or suggest adalimumab's effect on or distribution to all of the tissues affected by PsA, or how they may compare to the effect or distribution of infliximab or etanercept.

C. Mease 2000 (Ex. 1017)

Mease 2000 discusses the use of 25 mg of etanercept administered twice-weekly to treat PsA patients. (Ex. 1017, 2.) Mease 2000 does not disclose any clinical trials or results using adalimumab, any dosing regimen for adalimumab, or any connection between adalimumab and PsA. Mease 2000 also does not disclose or suggest adalimumab's effect on or distribution to all of the tissues affected by PsA, or how they may compare to the effect or distribution of infliximab or etanercept.

Mease 2000 explains that "[t]he few controlled trials assessing patients with psoriatic arthritis have not shown consistent efficacy" and that "response to therapy [for PsA derived from clinical experience in RA] is often unsatisfactory." (*Id*.) It describes "unique features" of PsA versus RA, "includ[ing] the potential for asymmetric, oligoarticular, axial and/or distal interphalangeal joint involvement, dactylitis, and enthesial inflammation." (*Id*.) Mease 2000 does not report whether etanercept would inhibit the progression of structural damage in PsA patients. (*See id.*, 6.)

D. Dechant (Ex. 1029)

Dechant discusses the use of infliximab to treat a small sample of 10 patients with PsA. (Ex. 1029, 8.) Patients in the study received 5 mg/kg infliximab at weeks 0, 2, and 6. After week 10, one patient stopped treatment and each remaining

patient's dose was personalized to an unspecified dose in the range of 3-4 mg/kg at an infusion interval of ≥8 weeks. (*Id*.) One patient received an increased dose at a shorter interval of 4 weeks after experiencing a flare. (*Id.*)

Dechant does not disclose using the approved RA dose (3 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter) for infliximab to treat PsA. (*See* Ex. 1027, 4.) Nor does it disclose or suggest a dosing regimen for adalimumab, any connection between adalimumab and PsA, or whether adalimumab could inhibit the progression of structural damage in PsA patients. Dechant also does not disclose or suggest adalimumab's effect on or distribution to all of the tissues affected by PsA, or how they may compare to the effect or distribution of infliximab or etanercept.

E. Rau (Ex. 1021)

As discussed in Section IX.C., *infra*, Petitioner has not established that the only version of Rau included with and cited by the Petition, Ex. 1021, is prior art. Ex. 1021 is an English translation of a review article that discusses studies of adalimumab to treat RA. (*See generally* Ex. 1021.) Rau does not disclose using adalimumab for any purpose other than to treat RA. Rau also does not disclose a 40 mg subcutaneous every-other-week fixed dose. Rau also does not discuss PsA or adalimumab's effect on or distribution to all of the tissues affected by PsA, much less a dosing regimen for treating patients with that condition. Rau includes

reports of the effect of doses of adalimumab of 1.0 mg/kg and higher on the Sharp Scores of patients with RA at 6 and 12 months, but does not address the *modified* Total Sharp Score for PsA or any specific measure of radiographic progression in PsA patients. (*Id.*, 7.)

F. Mease 2004 (Ex. 1056)

Mease 2004 is an abstract that reports results of a study of adalimumab to treat PsA patients performed by AbbVie's predecessor, Abbott Laboratories. The authors of Mease 2004 include Dr. Mark Weinberg, who is one of the named inventors on the '992 patent.

IV. The Patented Invention

The '992 patent discloses and claims novel methods for treating PsA. These methods comprise subcutaneously administering to a patient 40 mg of adalimumab every-other-week. (Ex. 1001, col. 55-56.)

Independent claims 1 and 2 of the '992 patent recite as follows:

> 1. A method of treatment of moderate to severe active psoriatic arthritis in adult patients, wherein each said patient has ≧3 swollen and ≧3 tender joints prior to the treatment and has failed NSAID therapy, comprising subcutaneously administering to each said patient 40 mg of adalimumab every other week, wherein 23% of said patients achieve 70% reduction in American College of Rheumatology (ACR) score at week 24 of the treatment.

> 2. A method for reducing or inhibiting symptoms in a patient with psoriatic arthritis, comprising subcutaneously administering to said patient 40 mg of adalimumab every other week.

(Ex. 1001, 55:18-29.) Dependent claims 5, 6, and 7 each depend from claim 2 and recite:

> 5. The method of claim 2, wherein the patient achieves at least a 50% reduction in ACR score at week 24 of the treatment.
>
> 6. The method of claim 5, wherein the patient achieves at least a 70% reduction in ACR score at week 24 of the treatment.
>
> 7. The method of claim 2, wherein said symptoms are progression of structural damage assessed by radiograph.

(Ex. 1001, 56:18-26.)

During prosecution, Patent Owner submitted references asserted by Petitioner (or a substantively identical version) to the Examiner via IDS, including Lorenz (Ex. 1028), Mease 2000 (Ex. 1017), Rau (Ex. 1021), Mease 2004 (Ex. 1056), and a version of Keystone (Ex. 1003). (Ex. 2002, 11, 12, 13, 15, 21.)

V. The Person of Ordinary Skill in the Art

Petitioner proposes a person of ordinary skill having an "M.D. and at least 3 years' post-residency experience treating patients for PsA and RA." (Pet., 14.) The definition of a person of ordinary skill, however, necessarily depends on the art of the claimed invention. *E.g.*, *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254,

1257 (Fed. Cir. 2007) (holding that, where the claims concerned a method for treating bacterial ear infections, one of ordinary skill would be a specialist with training and knowledge with ear treatments, not simply a general practitioner).

Here, the claims involve methods of treating PsA. (Ex. 1001.) Thus, for purposes of this preliminary response, Patent Owner does not contest that a person of ordinary skill in this art would have the skill set of a physician treating PsA patients or that such a physician would have an MD and at least three years of experience treating PsA patients. However, Petitioner fails to support its expansion of the definition of a POSA to a person with training in RA—a condition separate and distinct from that claimed. RA experience should therefore not be included in the POSA definition. For the reasons discussed below, however, Petitioner's unpatentability arguments fail regardless of whether this definition is adopted.

VI. Priority

With respect to its obviousness grounds (Grounds 2 and 3), Petitioner assumes all of the challenged claims are entitled to a priority date of July 18, 2003 (Ground 2) or July 19, 2002 (Ground 3). (Pet., 9.) For purposes of this preliminary response, Patent Owner does not dispute Petitioner's application of those alternative priority dates.

Petitioner suggests that claim 7 is entitled to an effective filing date of May 16, 2005, the date of U.S. Provisional App. No. 60/681,645. (*Id.*, 7.) But

Petitioner's arguments do not rely on that alleged priority date; rather, each obviousness ground assumes that claim 7 is entitled to an effective filing date of July 18, 2003 or earlier. (*Id.*, 9.) Because Petitioner's alleged priority date for claim 7 is not relevant to any of the asserted obviousness grounds, Patent Owner does not address it here.[2]

With respect to its anticipation ground (Ground 1), Petitioner argues that claims 1, 5, and 6 are entitled to an effective filing date of May 16, 2006, the date of U.S. App. No. 11/435,844. (Pet., 6, 13.) For the reasons discussed below in Section X, Petitioner's anticipation ground fails because its priority argument is irreconcilably inconsistent with its position regarding the scope of the claims.[3]

VII. Claim Construction

For the limited purposes of this preliminary response, Patent Owner does not contest Petitioner's proposed definition of the term "moderate to severe active psoriatic arthritis" or Petitioner's assertion that no other claim term requires a special meaning. (Pet., 14-15.) Patent Owner disputes, however, Petitioner's contentions that the preambles of claims 1 and 2 and the "wherein" clauses of claims 1, 5, 6, and 7 do not limit the claim. (*Id.*)

[2] Patent Owner reserves the right to dispute this alleged priority date for claim 7.

[3] As also noted below, Patent Owner reserves the right to establish an earlier priority date for claims 1, 5, and 6.

A. The Preambles of Claims 1 and 2 Are Limiting

The preambles of independent claims 1 and 2 recite "[a] method of treatment of moderate to severe active [PsA] in adult patients" and "[a] method for reducing signs or inhibiting symptoms in a patient with [PsA]," respectively. (Ex. 1001, 55:18-29.) These preambles substantively limit and provide antecedent basis for the claims because they are the only parts of the challenged independent claims that recite "psoriatic arthritis." (*Id*.) Moreover, claims 1 and 2 each refer to the patient recited in the preamble with the phrase "said patient," and dependent claim 7 further limits claim 2 with reference to "said symptoms." (*Id*.)

The case cited by Petitioner, *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003), confirms that a preamble is limiting where "the preamble provides antecedents for ensuing claim terms and limits the claims accordingly." Further, the "preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise." *Id.* Here, the preambles of claims 1 and 2 both provide antecedent basis and the essence of the invention (treating or "reducing or inhibiting" symptoms of psoriatic arthritis).

B. The Outcome Limitations of Claims 1, 5, 6, and 7 Are Limiting

Claims 1, 5, and 6 recite methods of treating PsA wherein a patient or population of patients achieve an ACR50 or ACR70 score at week 24 of treatment. (Ex. 1001, 55:18-29, 56:18-26.) Claim 7 recites a method of reducing or inhibiting symptoms of PsA "wherein the symptoms are progression of structural damage assessed by radiograph." (*Id.*, 56:25-26.)

Each of these recitations is a substantive limitation. First, with respect to claims 1, 5, and 6, by referring to "week 24 of the treatment," the claim language expressly requires at least a 24-week treatment duration. Otherwise, the reference to "week 24 of the treatment" would be superfluous. *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006) ("[C]laims are interpreted with an eye toward giving effect to all terms in the claim."). Second, claims 1, 5, 6, and 7 require that a patient or population of patients achieve at least an ACR50 or ACR70 response at week 24 (claims 1, 5, and 6) or that the method inhibit the progression of structural damage assessed by radiograph (claim 7), introducing a heightened efficacy requirement not otherwise found in the claim. These express limitations should be given meaning.

Petitioner's argument that the "structural damage" language of claim 7 does not "impart patentability" is vague and simply cross-references arguments made regarding the ACR outcomes of claims 1, 5, and 6. (Pet., 50-51, 56.) Petitioner has

not properly presented an argument that claim 7 is non-limiting. In any event, any such argument would be unavailing.

Petitioner fails to address any intrinsic evidence, including the claim language, specification, or prosecution history. (*Id*., 48-51, 56.) Instead, Petitioner relies solely on *Minton v. National Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373 (Fed. Cir. 2003). (Pet., 47-48.) This reliance is misplaced. The patent at issue in *Minton* claimed a method for trading securities "efficiently" on a computerized system. *Minton*, 336 F.3d at 1375, 1380. The Federal Circuit determined that the term "efficiently" was simply a "laudatory" term that did not limit how trades were executed, and that nothing in the specification or prosecution history suggested otherwise. *Id.* at 1381.

The ACR and structural damage limitations here are not analogous to the qualitative term "efficiently" in *Minton*. The ACR language limits claims 1, 5, and 6 by requiring both that a patient or patients be treated for at least 24 weeks and achieve an ACR50 or ACR70 level of treatment efficacy at week 24. The inhibition of progression of structural damage assessed by radiograph language limits claim 7 by requiring inhibition of those symptoms in the patient being treated. Unlike in *Minton*, these are substantive limitations.

VIII. Petitioner Has Not Established a Reasonable Likelihood of Prevailing as to Any Challenged Claim

A. Petitioner Fails to Establish That a POSA Would Have Had a Reasonable Expectation of Success of Using Adalimumab to Treat PsA

Petitioner argues that a POSA would have had a reasonable expectation of success that adalimumab would treat PsA based on (1) speculation that adalimumab may be a successful candidate for the treatment of diseases other than RA and (2) extrapolation from clinical results of *other drugs*. (Pet., 32-34, 51-53.) These arguments are insufficient to show a reasonable expectation of success. Among other deficiencies, Petitioner's cited references do not disclose or suggest that adalimumab would treat PsA, its analysis ignores the differences between RA and PsA, and Petitioner omits any mention of the multiple examples in which drugs that were known to treat RA were *not* effective in treating other diseases, such as PsA.

1. The Asserted Art Does Not Disclose or Suggest that Adalimumab Would Treat PsA

Petitioner repeatedly asserts that the prior art taught that "[a]dalimumab would be useful to treat PsA" and similarly that "adalimumab would effectively treat PsA." (*Id.*, 16, 43.) These assertions, however, are factually incorrect. *None* of the asserted or cited art discusses the efficacy of adalimumab to treat PsA.

a) The References in Petitioner's Grounds Do Not Disclose or Suggest Using Adalimumab to Treat PsA

The three references in Ground 3 do not discuss the use or efficacy of adalimumab to treat PsA. Keystone discusses using adalimumab for RA. (Ex. 1003, A481.) Dechant discusses the use of infliximab. (Ex. 1029, 8.) Mease 2000 discusses the use of etanercept. (Ex. 1017, 2.) None of these references discusses any connection between adalimumab and PsA, adalimumab's effect on or distribution to all of the tissues affected by PsA, or whether adalimumab could inhibit the progression of structural damage in PsA patients. The general disclosures in Dechant and Mease 2000 concerning the use of *other* drugs to treat PsA are insufficient to bridge this gap. Neither compares adalimumab to etanercept or infliximab at all, let alone compares them with respect to effect on or distribution to tissues affected by PsA or RA. As the Federal Circuit held in *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) merely identifying a "general approach that seemed to be a promising field of experimentation" is legally insufficient to establish a reasonable expectation of success. Here, the asserted references are silent about the drug at issue (*i.e.*, adalimumab) and do not even convey a general approach. *See id.* (finding no reasonable expectation of success "where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it"). Accordingly, Petitioner has failed to establish a reasonable expectation of success.

Ground 2 suffers from the same deficiency. In Ground 2, Petitioner combines Keystone and Mease 2000 with an additional reference, Lorenz. Petitioner's conclusion that Lorenz "clearly taught that adalimumab would be useful in treating PsA" (Pet., 44) is not supported by the reference. Lorenz separately mentions the *words* "D2E7" and "psoriatic arthritis," but nowhere states that D2E7 is a candidate for treating PsA, makes any connection between adalimumab and PsA, or discusses adalimumab's ability to inhibit progression of structural damage in PsA patients. Rather, Lorenz's PsA section only discusses anti-TNFα therapy with infliximab and etanercept—not adalimumab. (Ex. 1028, S18-19.)

Lorenz discusses adalimumab *only* in its "Summary" and "Rheumatoid arthritis and Crohn's disease" sections and *never* in connection with PsA. (*See generally* Ex. 1028.) In the "Summary" section, Lorenz speculates that "encouraging results *might* arise" in *rheumatoid arthritis* if clinical trials were conducted with adalimumab. (*Id.*, S17.)[4] In the "Rheumatoid arthritis and Crohn's disease" section, Lorenz states that developments in the treatment of other unidentified chronic inflammatory diseases "may include" additional clinical trials with new TNFα biologics, such as adalimumab. (*Id.*, S18.) Lorenz does not discuss whether or how adalimumab may affect or be distributed to all of the tissues

[4] All emphasis added unless otherwise noted.

affected by PsA, nor does it compare adalimumab's effect or distribution to that of etanercept or infliximab for PsA patients. In fact, Lorenz states that "long-term observations are *required* concerning side effects and efficacy of…agents [including adalimumab]." (*Id.*, S18.) It notes specifically that such further observations are required for "radiological progression." (*Id.*)

Lorenz's broad speculation about potential uses of anti-TNF agents was contradicted by real-world results. Petitioner's declarant, Dr. Helfgott, states, for example, that Lorenz "predicted" etanercept's approval in the treatment of Crohn's disease. (Ex. 1002, ¶ 39.) Dr. Helfgott fails to address, however, that Sandborn reported in 2001 that etanercept was *ineffective* in treating Crohn's disease. (Ex. 2013, 6.) Lorenz also mentions the development of other TNFα inhibitors such as onercept. (Ex. 1028, S18.) But Phase 3 trials of onercept were later discontinued and the drug was never approved for treating psoriatic arthritis. (Ex. 2014, 1.) Pegsunercept, another TNF inhibitor mentioned by Lorenz, was also never approved for PsA. (*See* Ex. 2015, 13; Ex. 2016, 1-7.) Lorenz also lists multiple potential "new indications" for TNFα therapy (Ex. 1028, S18-21), but in practice not all anti-TNFα agents in fact treated all of those indications. For example, despite being listed in Lorenz, a study showed that etanercept was "not effective" in maintaining remission in Wegener's granulomatosis patients. (Ex. 2018, 351.)

b) Petitioner's Attempt to Rely on "Background" References Is Unavailing

In addition to the asserted prior art, Petitioner discusses references that are not part of its prior art grounds to purportedly "confirm[] that a POSA would understand Lorenz … as teaching the use of D2E7 to treat PsA." (*See* Pet., 23, 32, 44.) Petitioner has failed to meet its burden to show that multiple of these references qualify as prior art. Moreover, this attempted reliance on "background" references highlights the weakness of the arguments in Petitioner's grounds and runs afoul of the Board's requirement to precisely identify the art relied upon. *See* 37 C.F.R. § 42.104(b).

(1) Petitioner Has Failed to Establish the "Background" References Are Prior Art

Petitioner asserts that Japan Chemical Week and the Press Release qualify as prior art either under 35 U.S.C. § 102(a) or (b), but provides no evidence that they were publicly available. (Pet., vii, xi, xii, 24-25.) Even for these alleged "background" references, Petitioner must meet its burden of making a threshold showing that alleged prior art was available as a printed publication. *See Coal. for Affordable Drugs IV LLC v. Pharmacyclics, Inc.*, IPR2015-01076, Paper 33 at 5-6 (P.T.A.B. Oct. 19, 2015). Here, Petitioner has failed to do so. Because institution decisions must be based on information in the petition, this deficiency cannot be

remedied. 35 U.S.C. § 314(a); *Actavis, Inc. v. Research Corp. Tech., Inc.*, IPR2014-01126, Paper 22 at 13 (P.T.A.B. Jan. 9, 2015).

Petitioner asserts a publication date of September 13, 2001 for Japan Chemical Week, but cites only the exhibit itself with no evidence as to its source (Dow Jones, Japan Chemical Week, or Factiva) and provides no evidence as to its publication, dissemination, or public availability. (Pet., xi, 24.) The September 13, 2001 date printed on the exhibit, alone, is insufficient to establish public availability. *See LG Elecs., Inc. v. Advanced Micro Devices, Inc.*, IPR2015-00329, Paper 13 at 13 (P.T.A.B. July 10, 2015). Indeed, Petitioner fails to reconcile this date with the other dates listed on the exhibit—May 28, 2014 and a 2014 copyright date. (Ex. 1034, 2.) Petitioner thus has not shown that Exhibit 1034 qualifies as a printed publication as of September 13, 2001.

Similarly, Petitioner characterizes Exhibit 1049 as an "AbbVie Press Release" published on March 3, 2003, but cites only the exhibit itself with no evidence as to its source, publication, dissemination, or public availability. (Pet., xii-xiii, 24-25.) Compounding Petitioner's failure, Exhibit 1049 appears not to be a press release directly from AbbVie, as Petitioner implies, but rather an Internet Archive Wayback Machine search result for an "Immune Tolerance Network" webpage. (Ex. 1049, 1-2.) Petitioner does not address whether the webpage was available on March 3, 2003, and, moreover, mere availability on a website is not

enough to establish public accessibility. *Celltrion, LLC v. Biogen, Inc.*, IPR2017-01230, Paper 10 at 13-15 (P.T.A.B. Oct. 12, 2017). Petitioner also provides no evidence establishing: whether the webpage was indexed; whether an interested person would have been aware of the web address; how the Wayback Machine archives webpages; or how archiving through this site relates to public availability. *See Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349-50 (Fed. Cir. 2016) (reference was not publicly accessible because no evidence showed that an interested person would be aware of the web address or that an Internet search would have located the reference). Petitioner thus has not shown that Exhibit 1049 was published on March 3, 2003.

(2) Petitioner's "Background" References Do Not Disclose or Suggest Using Adalimumab to Treat PsA

Even if Petitioner's "background" references are considered, they too fail to disclose or suggest that adalimumab would treat PsA. Petitioner first cites Japan Chemical Week, a summary article providing analysis of the TNFα inhibitor market. (Ex. 1034.) Petitioner's statement that the reference "identified adalimumab . . . as [a] TNF-α inhibitor[] that would be used to treat not only RA, but also PsA and psoriasis" is simply incorrect. (Pet., 32.) Japan Chemical Week *does not mention PsA* in discussing adalimumab. (*See* Ex. 1034, 1.) It also does not mention inhibition of progression of structural damage for any disease. (*See id*.)

Rather, the article discusses adalimumab only in relation to other diseases and generally mentions PsA as a TNFα mediated disease. Japan Chemical Week therefore cannot remedy any of the deficiencies in Lorenz discussed above. (Pet., 44.)

Petitioner's reliance on a Press Release (Ex. 1049) is similarly insufficient. (*See* Pet., 24-25, 44.) The Press Release describes work by Patent Owner's predecessor, Abbott Laboratories, regarding the initiation of a PsA clinical trial using HUMIRA®. (Ex. 1049, 1-2.) It does not describe any dosing regimen for adalimumab or any results in PsA (including whether adalimumab inhibited progression of structural damage). Instead it merely states the trial will attempt to "help … understand the effect of HUMIRA in [PsA]." (Ex. 1049, 1.) This is not enough to establish a reasonable expectation of success. As stated in *Abbott Laboratories v. Sandoz, Inc.*, "*KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try.'" 544 F.3d 1341, 1352 (Fed. Cir. 2008). Moreover, Petitioner fails to explain how the initiation of the adalimumab PsA clinical trial mentioned in the Press Release (Ex. 1049), could "confirm" that Lorenz connects D2E7 to PsA (Pet., 44) when, as discussed above, Lorenz makes no such connection.

c) Petitioner's Reliance on Disclosure of Other Drugs Is Insufficient to Disclose or Suggest Treatment of PsA With Adalimumab

For both of its obviousness grounds (Grounds 2 and 3), Petitioner argues that because various references showed efficacy of *different drugs*, namely infliximab and etanercept, in treating PsA, a POSA would "know that…adalimumab was a prime candidate for treating PsA." (Pet., 55, 43-44.) This simplistic analysis ignores the substantial complexity of PsA and differences between adalimumab and other anti-TNFα agents. It also suffers from the same conflation of *potential* use with reasonable expectation of successfully treating PsA that plagues Petitioner's arguments with respect to Lorenz.

Specifically, Petitioner fails adequately to explain why results with infliximab and/or etanercept would have been imputed to adalimumab. There is substantial diversity among the structures of the fully human antibody adalimumab (Ex. 1003, A481), chimeric antibody infliximab (Ex. 1027, 2), and fusion protein etanercept (Ex. 1006, 1.) And the drugs are administered in different ways, with both variable weight-based dosing for infliximab (Ex. 1027, 2), and more frequent subcutaneous dosing for etanercept (Ex. 1006, 10). Petitioner does not address any differences in the respective tissue distribution or pharmacokinetic properties of these drugs. Particularly in view of the evidence (*see* Section VIII.A.2.b, *infra*) that not all anti-TNFα inhibitors treat all diseases implicating TNFα, Petitioner's

reliance on experience with drugs other than adalimumab is insufficient to establish a reasonable expectation of success.

2. Petitioner Fails to Address the Differences Between PsA and RA and Their Respective Treatments

Petitioner has not shown a reasonable expectation of success because it omits any discussion of the differences between PsA and RA and their respective treatments. Petitioner relies on purported high-level categorical similarities between RA and PsA to argue that, because adalimumab was shown to be effective in treating RA, a POSA would have had a reasonable expectation that adalimumab would also treat PsA. (Pet., 30-34, 52-53.) But, as described in Section II.B., *supra*, the signs, symptoms, and affected tissues of RA are *different* in multiple respects from those of PsA, and it was known that not all anti-TNFα inhibitors were shown to be effective in treating all diseases thought to implicate TNFα.

When a party presents conclusory, oversimplified arguments attempting to extrapolate from a treatment in one disease to another, institution should be denied. *Dr. Reddy's Labs., Ltd. v. Galderma Labs., Inc.*, IPR2015-01782, Paper 10 at 18 (P.T.A.B. Feb. 16, 2016). In *Dr. Reddy's*, for example, the Board denied institution because one would not have reasonably expected to successfully use a specific dose of a periodontal-disease drug to treat a different condition, rosacea, based on an allegedly common inflammatory pathway. *Id*. at 15-16. These two different conditions affected distinct organ systems: periodontal disease affected the gums in

the mouth while rosacea affected the skin. *Id.* at 17-18. Each disease required a different medical specialty for treatment. *Id*. at 17. And the etiology of rosacea was unknown. *Id*. at 15-16. Thus, the Board found no reasonable expectation of success for applying a treatment from one disease "to a different disease in a different tissue type." *Id*. at 19-22. The same reasoning supports denying institution here. *See also Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1337-38 (Fed. Cir. 2010) (rejecting argument that prior art use of autoimmune drug would render method of treating osteoporosis obvious). Significantly, Petitioner cites no case finding a reasonable expectation of success by extrapolating from a treatment in one disease to a different disease.

a) RA and PsA Are Different Diseases

Petitioner's arguments fail to address that RA and PsA are different in multiple respects. As discussed in Section II.B., *supra*, RA and PsA affect different tissues, have different pathologies, result in different symptoms, have different subtypes, and cause different deformities.

The differences between RA and PsA were articulated in the alleged prior art cited by Petitioner. The Press Release, for example, explained that "[t]he arthritic manifestations [of PsA] often include not only debilitating disease of the hands and feet as is seen in [RA], ***but also*** arthritis of the spine and painful inflammation of tendon insertions [enthesitis]." (Ex. 1049, 1.) The Press Release

also explained that PsA patients "experience the often unmanageable symptoms of arthritis combined with psoriasis" and have symptoms that include "varying degrees of psoriasis" (*id.*, 1), which are not characteristic of RA. Mease 2000 also acknowledges that "unique features" of PsA as compared to RA "include the potential for asymmetric, oligoarticular, axial and/or distal interphalangeal joint involvement, dactylitis, and enthesial inflammation." (Ex. 1017, 2.) Petitioner does not discuss either passage, let alone address the differences between the diseases.

b) RA Treatments Do Not Consistently Work in PsA and Anti-TNFα Agents Do Not Consistently Work in All Diseases Implicating TNFα

Petitioner also ignores multiple examples demonstrating that an RA drug will not necessarily treat PsA. As described in Section II.C., above, small molecule treatments such as gold, sulfasalazine, corticosteroids, and hydroxychloroquine that were used to treat RA were "unsatisfactory" or contraindicated in PsA. And multiple biologic drugs—including rituximab, anakinra, and tocilizumab—were effective in treating RA but were not shown to be effective in PsA studies.

Furthermore, it was known as early as 2001 that not all anti-TNFα inhibitors worked to treat all diseases thought to implicate TNFα. For example, a clinical trial of etanercept, previously shown effective in treating RA, failed to show that it was

effective in treating Crohn's disease. (Ex. 2013, 6.)[5] And, another "strong suppressor of TNFα," oxpentifylline, also failed to treat Crohn's disease. (Ex. 2020, 470-71.) In 2003, another anti-TNFα agent, CDP571, was abandoned by its developer after the drug was shown to have "no discernible benefits" in the long-term treatment of Crohn's disease. (Ex. 2019, 14.) Etanercept was also shown to not be effective in inducing remission of Wegener's granulomatosis. (Ex. 2018, 351.) As the Federal Circuit has recognized, "there can be little better evidence negating an expectation of success than actual reports of failure." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1081 (Fed. Cir. 2012)) (quoting *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003)).

Petitioner's reliance on Lorenz's statement that the "*current* therapeutic approaches for PsA are similar to those for RA" is unavailing. (Pet., 22.) That some existing approaches to therapy were "similar" for RA and PsA does not mean that all therapies will be similar, let alone the same. Indeed, Petitioner fails to address statements in the art that a POSA could not equate "the efficacy and safety

[5] As explained in Section VIII.A., *supra*, Lorenz incorrectly speculated that etanercept would be effective to treat Crohn's Disease, a premise that was disproven before the invention of the '992 patent. (*See* Ex. 1028, S17-18; Ex. 2013, 6.)

of an agent in RA" with "efficacy and safety in PsA" because "PsA and RA are distinct diseases." (Ex. 2005, 29.) Petitioner also does not address statements in the art that "therapies above those developed for RA" might "well be…required" to manage the unique problems of PsA. (Ex. 2009, 1519.)

B. Petitioner Fails to Establish That a POSA Would Have Had a Reasonable Expectation That 40 mg of Adalimumab Every-Other-Week Would Treat PsA

Petitioner's obviousness grounds depend on the premise that a POSA would have had a reasonable expectation of success in using *the same* adalimumab dose to treat PsA as had been used to treat RA (40 mg every-other-week). But, by Petitioner's admission, not all drugs used to treat both RA and PsA were used at the same dose to treat both diseases. Petitioner repeatedly acknowledges that the other drugs it cites used "the same *or similar*" dosing regimens for RA and PsA. (*E.g.*, Pet., 45.) But "the same" and "similar" are two different things.[6] Petitioner's attempt to gloss over these differences is fatal to its grounds.

1. Infliximab and Etanercept Dosing Confirms the Uncertainty of Dosing in the Art

Petitioner's cited art demonstrates that infliximab was used at different doses, not "the same" dose, to treat RA and PsA. Petitioner's Ground 2 relies on

[6] Petitioner does not explain what a "similar" dose means or how a "similar" dose is relevant in the context of its obviousness analysis.

Lorenz, which describes multiple studies that tested 5 mg/kg of infliximab for the treatment of PsA. (Ex. 1028, S18-19.) This 5 mg/kg infliximab dose was also used to treat PsA in Dechant, which forms the basis of Petitioner's Ground 3. (Ex. 1029, 8.) A 5 mg/kg dose was also used to treat PsA in the Van den Bosch (Ex. 1037, 429) and Ogilvie (Ex. 1033, 6) references cited in Petitioner's Table 2. (Pet., 38.) But 5 mg/kg is not the same as the 3 mg/kg infliximab dose approved by the FDA for the treatment of RA. (*See* Ex. 1027, 2, 4.) Petitioner does not explain why or how the repeated disclosures in the prior art of dosing infliximab at a *different* amount when tested in PsA than it was in RA would lead a POSA to reasonably expect that the *same* dose of adalimumab would work to treat both RA and PsA.

Petitioner's citation to multiple references with additional different infliximab dosing regimens only confirms the uncertainty regarding dosing for PsA in the art.[7] (*See* Ex. 1004, 6 (Marzo-Ortega) (3 mg/kg); Ex. 1050 (Wollina) (more frequent dosing than RA (*compare* Ex. 1050, 7, *with* Ex. 1027, 4; Pet., 37-38.)); Ex. 1029, 8 (Dechant) (5 mg/kg followed by personalized doses of 3-4 mg/kg at individualized intervals).) In view of this considerable uncertainty, Petitioner's failure to explain how a POSA would evaluate the *different* PsA dose disclosed in

[7] With respect to Dechant, Petitioner cannot show that its dosing scheme was "shown to be effective in treating RA" (Pet., 38, 55) because Petitioner has not pointed to any study of infliximab in RA that used Dechant's dosing scheme.

Lorenz—the only infliximab reference that forms a part of its ground—with this conflicting art defeats its argument that a POSA would reasonably expect the *same* adalimumab dose used in RA to work in PsA.

Petitioner's citation to dosing of etanercept, does not alter this conclusion. (*See* Ex. 1017 (Mease 2000); Ex. 1028, S19 (citing Mease 2000).) As a threshold matter, as with infliximab, Petitioner has pointed to nothing in its cited references that compares etanercept's effect on or distribution to all of the tissues affected by PsA with that in tissues affected by RA. Nor has it identified a comparison of etanercept's effect or distribution with that of adalimumab in any disease. Moreover, even if etanercept and infliximab were instructive with respect to adalimumab dosing,[8] the inconsistency in dosing among the agents contributes to

[8] Petitioner has not demonstrated that they are. Each of these agents is different from adalimumab in terms of (among other things) structure, dosing regimen, and pharmacokinetics. In view of this, Petitioner's simplistic argument that because all three drugs are anti-TNFα agents, disclosures about dosing of two of them should be imputed to the third is facially insufficient. For example, Petitioner fails to establish that the distribution or effect on all of the tissues affected by PsA from such weight-based, intravenously administered infliximab dosing (which could involve administering 500 mg to 1,000 mg per dose depending on patient weight)

the uncertainty in the art, and the unpredictability of dosing for a separate, unique agent. Petitioner's attempt to cherry-pick an example from the prior art that it believes supports its position while ignoring abundant examples to the contrary does not support a reasonable expectation of success and should be rejected.

2. Petitioner's List of Small Molecule Drugs Is Irrelevant and Incomplete

Petitioner's citation to a select list of small molecules and their dosing regimens likewise does not save its reasonable expectation arguments. Although not part of its grounds and therefore not properly incorporated into argument, Petitioner relies on a list of steroids in Table 3 for the proposition that "small molecule drugs [were] used to treat RA and PsA at the same or similar dose[s]." (Pet., 40, 45.) As an initial matter, Petitioner provides no scientific rationale for why a POSA would have assumed that any similarity in dosing for small molecule drugs would apply for biologics like adalimumab. Moreover, Petitioner's Table 3 does not support its argument. The labels for Hydrocortone, Cortone, Decadron, Prelone, Solu-medrol, and Celestone state that their dosages vary depending on the disease. (Ex. 1035, 27, 20, 24, 33, 38, 42.) They do not state that the same dose was used for PsA and RA, and Petitioner has not shown that they were. (*See id*.)

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was comparable to or predictive of the distribution or effect of subcutaneously administering much smaller doses of 40 mg of adalimumab.

And, as described in Section II.C., *supra*, Petitioner omits the material fact that corticosteroids, including those cited in Table 3, were *contraindicated* for patients with skin disease, such as psoriatic arthritis patients. (Ex. 2009, 1515.) Petitioner has not reconciled this fact with its argument that a POSA would look to these same steroids for guidance on dosing adalimumab.

Moreover, Petitioner's premise that small molecule drugs were used to treat RA and PsA at the same or similar doses is expressly refuted by the small molecule drug methotrexate, which Petitioner omits from its Table 3. Methotrexate is noted as combination therapy for PsA in multiple of Petitioner's cited studies (*see* Pet., 37-39 (Table 2)), and was used at a *different* dose for the treatment of PsA (*e.g.*, 15-25 mg/week (Ex. 1004, 6)) than that approved in RA (7.5 mg/week (Ex. 2021, 10)).

Accordingly, Petitioner fails to establish that a POSA would have been motivated to use the 40 mg every-other-week dose of adalimumab for RA taught by Keystone to treat PsA with a reasonable expectation of success. The Petition should therefore be denied.

IX. Petitioner Has Not Established a Reasonable Likelihood of Prevailing on Dependent Claim 7

Claim 7 recites a method of reducing or inhibiting the progression of structural damage assessed by radiograph in a PsA patient by administering 40 mg of adalimumab every-other-week. (Ex. 1001, 56:25-26.) Petitioner fails to establish

that claim 7 would have been obvious under either of its two theories: (1) that the claim would have been obvious based on the disclosure of Rau or Lorenz or (2) that the efficacy requirement was inherent from the teachings of the prior art.

A. Petitioner's Obviousness Arguments Are Deficient and Inconsistent with Its Cited References

In its obviousness grounds, Petitioner cites results from studies of adalimumab to treat RA (Ground 3) or infliximab to treat RA (Ground 2) in support of its argument that a POSA would have reasonably expected that adalimumab administered at 40 mg every-other-week in PsA patients would inhibit the progression of structural damage as required by claim 7. (Pet., 51-52, 56-57.) These arguments are insufficient and inconsistent with Petitioner's cited references.

1. Petitioner Has Not Established a Reasonable Expectation of Success of Inhibiting the Progression of Structural Damage

For at least three reasons, Petitioner has failed to establish that a POSA would have had a reasonable expectation of successfully inhibiting the progression of structural damage in PsA patients using 40 mg every-other-week of adalimumab.

First, none of Petitioner's cited references discloses inhibition of structural damage in *PsA* with *any agent*. The *only* disclosure relied upon by Petitioner relates to RA. The omission of any relevant *PsA* disclosure is important in view of

the multiple differences in joint disease and progression of structural damage in patients with RA and PsA, as discussed above. (*See* Section II.B., *supra*.) In particular, those in the art recognized that:

> Radiographic progression [in PsA], when it occurs in the mutilating forms, can proceed rapidly and is poorly understood. The ankylosis, bone lysis and new bone formation are very particular to PsA and not commonly seen in RA. They are responsible for a large degree of the long-term loss of function and disability in these patients and it may well be that specific new therapies above those developed for RA will be required to manage these problems.

(Ex. 2009, 1519.) The differences in RA and PsA were reflected in differences in the tests used to measure radiographic progression in each of them. Thus, for example, whereas the Sharp score was used to measure radiographic progression in RA, a modified Sharp score ("mTSS") was used to evaluate radiographic progression in PsA. (*See* Ex. 2001, ii62-63.) The mTSS score used in PsA measured *additional* parameters than those measured for RA, meaning that the scores could not simply be substituted for one another. (*See id*.) Petitioner's suggestion that a POSA would thus assume based on Sharp scoring in one disease that an agent would result in successful *modified* Sharp scoring in a different disease is entirely unsupported.

Second, Petitioner's cited art explicitly noted that the ability of an anti-TNFα agent to inhibit progression of structural damage could not be reasonably expected by one of ordinary skill. Lorenz states that in RA "[f]urther long-term observations are required…focusing particularly on radiological progression under therapy with anti-TNF agents in combination with methotrexate….[and] specifically for the combinations of etanercept plus methotrexate and D2E7 plus methotrexate in patients with RA." (Ex. 1028, S18.) Lorenz thus expressly declines to make even part of the logical leap urged by Petitioner—that because one anti-TNFα agent (infliximab) could inhibit progression of structural damage in a particular disease (RA), that another (adalimumab) could as well. Petitioner does not address this passage, let alone explain how a POSA could have reasonably expected adalimumab to inhibit progression of structural damage in patients in a *different disease* (PsA) based on Lorenz.

Mease 2000 similarly urges additional study of radiographic progression, stating that, "[f]urther study in this population would be useful" and "[w]hether etanercept would improve articular damage measured radiographically should be examined." (Ex. 1017, 6.) Thus, contrary to Petitioner's hindsight-driven theory, Mease and Lorenz explain that, with respect to inhibition of structural damage, a POSA could not simply reasonably expect success based on results in RA, results

in another agent, or, indeed, results in PsA with the same agent. This defeats Petitioner's obviousness theory with respect to claim 7.

Third, Petitioner ignores that inhibition of the progression of structural damage assessed by radiograph is a significant efficacy outcome that is far from routine or expected. The FDA has a separate indication for reducing or inhibiting the progression of structural damage in patients with PsA. (*See, e.g.*, Ex. 2022, 1 (FDA letter separately approving "new indication[] for inhibiting the progression of structural damage" in PsA patients for HUMIRA®).) And not all drugs used to treat PsA are used for this separate indication. For example, although methotrexate is used to treat PsA (at a different dose than RA), studies showed that it does not successfully inhibit the progression of structural damage. (Ex. 1023, 5.)

In sum, Petitioner's failure to cite any reference disclosing that any agent successfully inhibited the progression of structural damage in PsA patients, its omission of discussion of uncertainty and requests for further analysis called for by its cited references, and its failure to address the difficulty of achieving the claimed outcome, demonstrate that Petitioner has not shown a motivation to combine the cited references with a reasonable expectation of success.

2. **Petitioner Fails to Address the Claimed Dose**

With respect to Ground 3, Petitioner cites Rau (which, as discussed *infra*, Petitioner has not established is prior art) and argues that because Rau "reported

that adalimumab treatment inhibited progression of structural damage … in *RA* patients," a "POSA would have expected similar inhibition of the progression of structural damage in PsA patients treated with adalimumab." (Pet., 56-57.) Dr. Helfgott attempts to justify this conclusion by summarily arguing that a POSA would expect this outcome because RA and PsA are "similar[]." (Ex. 1002, ¶ 156.)

Among other deficiencies, Petitioner's argument is entirely silent with respect to *dose*. This is an important omission. Rau reports results from a study of adalimumab to treat RA at multiple intravenous weight-based doses, *not* the claimed fixed subcutaneous 40 mg every-other-week dose. (*See* Ex. 1021, 5.) Petitioner nowhere argues that any particular weight-based dose in Rau would be instructive as the outcome to be expected for any particular fixed dose, let alone 40 mg every-other-week.

In fact, Rau at most shows that adalimumab inhibited radiographic progression in RA patients at *higher* doses than the claimed 40 mg every-other-week. Table 3 of Rau, for example, reports, *e.g.*, Sharp Erosion Score data at 6 months and 12 months for patients in study DE003. (*Id.*, 7.) Figures 4 and 5, however, demonstrate that at *12 weeks*, *i.e.*, well before the 6-month data in Table 3 relied upon by Petitioner was collected, no patient in the 0.5 mg/kg arm of the DE003 study remained in the study. (*Id.*, 6-7.) Thus, Rau cannot and does not support that adalimumab had any effect on structural damage in RA patients

receiving 0.5 mg/kg (or, hypothetically, an intravenous dose of 40 mg for an 80 kg patient).[9] At the very most, the data collected in Rau and cited by Petitioner would support that an intravenous dose of 1.0 mg/kg or higher was needed to inhibit structural damage in RA patients. By way of example, an 80 kg patient receiving 1.0 mg/kg, would have received 80 mg intravenously. Moreover, because drug was readministered only upon disease flare, the DE003 study in Rau did not disclose a standard every-other-week dosing interval. (*See id.*, 5, Table 1.) Such data do not support Petitioner's claim that a POSA would expect that a 40 mg every-other-week subcutaneous dose would successfully inhibit progression of structural damage in RA patients—let alone in PsA patients.

Petitioner's Ground 2 suffers from a similar deficiency. There, Petitioner cites Lorenz's summary disclosure that a study of infliximab plus methotrexate showed no median radiological progression over 12 months in treating RA. (Pet., 51.) Neither Petitioner nor Lorenz, however, discusses at what *dose* such results were achieved. Even if Lorenz's disclosure were sufficient to teach that administration of adalimumab could reasonably be expected to inhibit progression

[9] Patent Owner does not concede that any particular weight-based dose can be assumed to equal a particular fixed subcutaneous dose. Nor does Patent Owner concede that the amount of an intravenous dose is equivalent to the amount of a subcutaneous dose.

of structural damage in PsA, which it does not, this is a fatal omission. Claim 7 requires not only that adalimumab inhibit progression of structural damage in PsA patients, but that it do so at a dose of 40 mg every-other-week. In the absence of any discussion about the dose at which the alleged prior art achieved the cited result, Petitioner's grounds regarding claim 7 should be denied.

B. Petitioner Has Failed to Establish that the Claimed Structural Damage Outcome Is Inherent

Petitioner alternatively argues that the structural damage outcome is an inherent result of practicing the claimed method. (Pet., 50-51.) Petitioner's narrative argument is entirely conclusory: it does not cite data reflecting that any patient treated according to the claimed method would necessarily achieve the claimed structural damage outcome, and Dr. Helfgott does not address this inherency theory in his declaration. (*See* Pet., 50; Ex. 1002, ¶¶ 139-41, 155-57.)

Despite omitting such data from its argument, Petitioner includes a single citation to the specification of the '992 patent in its purported "summary of invalidity grounds." (Pet., 65-66.) Here, it states that the '992 patent reports "that '[a]dalimumab was more effective compared with placebo in inhibiting radiographic disease progression over a 24-week period' in PsA patients receiving 40 mg adalimumab eow." (*Id.*) Even if the Board credits this single, unsupported citation as an inherency argument, it fails because it does not establish that the limitation is *necessarily present*. To the contrary, the '992 patent at most

demonstrates that *some* patients experienced inhibition of structural damage. (*See* Ex. 1001, 38:53-40:33, Figs. 2-3.) This is legally insufficient to establish inherency. "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient" to establish inherency. *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (quoting *In re Rijckaert*, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993)). Inherency "may not be established by probabilities or possibilities." *Id.* (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). Petitioner thus fails to establish that the inhibition of structural damage outcome of claim 7 is "necessarily" present, as required for inherency.

C. Petitioner Has Not Established that Rau (Ground 3) Is Prior Art

Petitioner's exhibit list asserts that Rau (Ex. 1021) is prior art under § 102(b) and appears to assert it was published in 2000. (Pet., ix.)[10] Exhibit 1021, however,

[10] Petitioner certifies that the Petition is 13,987 words, but this total appears to omit the conclusion (40 words) and signature block (35 words), and significantly, the footnotes in the Exhibit list (172 words) that contain arguments regarding documents' publication status (Pet., vii-xiv). To the extent Petitioner seeks to rely on these arguments or the exhibits cited therein (the exhibit list being the only place Exhibits 1007, 1008, 1013, 1015, 1022, 1024, 1032, 1036, 1038, 1041, 1048, 1052, 1054, 1055, 1057, 1059, and 1060 are cited), the Petition violates both the word count limit and the prohibition against incorporation by reference. 37 C.F.R.

is an English language translation prepared in *2015*, and is therefore *not* prior art to the ’992 patent. (Ex. 1021, 11.) Ground 3 should therefore be denied as not being based on a prior art printed publication. 35 U.S.C. § 311(b). Because institution decisions must be based on information in the petition, this deficiency cannot be remedied. 35 U.S.C. § 314(a); *Actavis, Inc. v. Research Corp. Tech., Inc.*, IPR2014-01126, Paper 22 at 13 (P.T.A.B. Jan. 9, 2015). Moreover, even if Petitioner intended to rely on the 2000 date of the original German version of the Rau paper, it failed to include a copy of that document with the Petition, thereby failing to meet the statutory requirement under 35 U.S.C. § 312(a)(3)(A). *See also* 37 C.F.R. §§ 42.104(b)(2), 42.105(a).

X. Petitioner’s Inconsistent Arguments Regarding ACR Outcomes Warrant Denial of Its Anticipation Challenge

In Ground 1, Petitioner argues anticipation with regard to claims 1, 5, and 6, which recite certain ACR outcomes. This anticipation challenge should be denied because it is irreconcilable with Petitioner’s position regarding the effect of the ACR outcome language in the claims.

Petitioner first argues that the earliest effective filing date of claims 1, 5, and 6 is the date that specific ACR outcomes were allegedly added to the specification

§ 42.24(a)(i); 37 C.F.R. § 42.6(a)(3).

of priority application 11/435,844. (Pet., 6; *see also id*., 9, 16.)[11] Separately, however, Petitioner argues that the ACR outcomes are "statements of intended result that cannot impart patentability." (Pet., 48.) Petitioner thus seeks to have it both ways—arguing that the ACR outcomes are limiting where they help the petition (establishing a later priority date) but that they are not limiting where they hurt the petition (reading the prior art onto the claims). Petitioner does not acknowledge, let alone reconcile, this inconsistency.

Petitioner's inconsistency cannot be squared with the law. That which is non-limiting does not require written-description support: "An applicant complies with the written description requirement by describing the invention, with all its claimed *limitations*." *Lochner Tech., LLC v. Vizio, Inc.*, 567 F. App'x 931, 937 (Fed. Cir. 2014) (citation omitted); *see also id.* at 939 ("[T]here is no precedent

[11] Notably, Petitioner did not attach the '844 application as an exhibit to its petition. Accordingly, Petitioner has not provided evidence establishing its priority argument, and its anticipation challenge should be denied. *See, e.g.*, *Cisco Sys., Inc. v. Custom Media Tech. LLC*, IPR2014-01272, Paper 9 at 22-23 (P.T.A.B. Jan. 30, 2015) (denying institution where petitioner failed to attach material exhibit). A petitioner "should not expect the Board to search the record and piece together what may support [petitioner's] arguments." *Dominion Dealer Sols., LLC v. AutoAlert, Inc.*, IPR2013-00223, Paper 14 at 4 (P.T.A.B. Oct. 10, 2013).

requiring a patentee to disclose or enable unclaimed elements."); *see also Hyatt v. Dudas*, 492 F.3d 1365, 1370-71 & n.4 (Fed. Cir. 2007). Thus, if Petitioner is correct that the ACR outcomes are not limiting, it cannot rely on the presence or absence of those outcomes to establish a later priority date.[12]

Petitioner's internally inconsistent arguments are thus insufficient to support its anticipation challenge. "It is not the responsibility of the Board to reconcile Petitioner's conflicting arguments and evidence." *Xilinx, Inc. v. PLL Tech., Inc.*, IPR2015-00148, Paper 8 at 29 (P.T.A.B. Apr. 28, 2015) (denying institution because "Petitioner's contentions regarding anticipation … conflict with each other"). Instead, the Board routinely denies institution where a petitioner adopts self-defeating arguments. *See, e.g.*, *ams AG v. 511 Innovations, Inc.*, IPR2016-01793, Paper 15 at 15 (P.T.A.B. Mar. 15, 2017) (denying institution in part because of "Petitioner's inconsistent treatment of … [a] limitation"); *Baxter Healthcare Corp., v. Millenium Biologix, LLC*, IPR2013-00583, Paper 9 at 7 (P.T.A.B. Mar. 21, 2014) (denying institution, "emphasiz[ing] the inconsistency of

[12] If the Board allows Petitioner's inconsistent anticipation ground to proceed to trial, Patent Owner reserves the right to, *inter alia*, establish that Mease 2004 is not § 102 prior art; that claims 1, 5, and 6 are entitled to an effective priority date before May 16, 2006; and/or that the inventors conceived of and diligently reduced the claimed inventions to practice before publication of Mease 2004.

Petitioners' argument here with their argument [elsewhere]"); *see also Apple Inc. v. California Inst. of Tech.*, IPR2017-00701, Paper 14 at 19 (P.T.A.B. Aug. 8, 2017) (denying institution in part because of Petitioner's "inconsistent … analysis" of it and another claim). The Board should follow course here and decline to institute Ground 1.

XI. Conclusion

Petitioner has not established a reasonable likelihood of prevailing as to any challenged claim of the '992 patent. The Board should therefore deny institution of the Petition.

Respectfully submitted,

Dated: January 5, 2018

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** contains 11,332 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and Exhibits 2001-2023 were served electronically via email on January 5, 2018, in their entirety on the following:

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